Structural identifiability of parallel pharmacokinetic experiments as constrained systems

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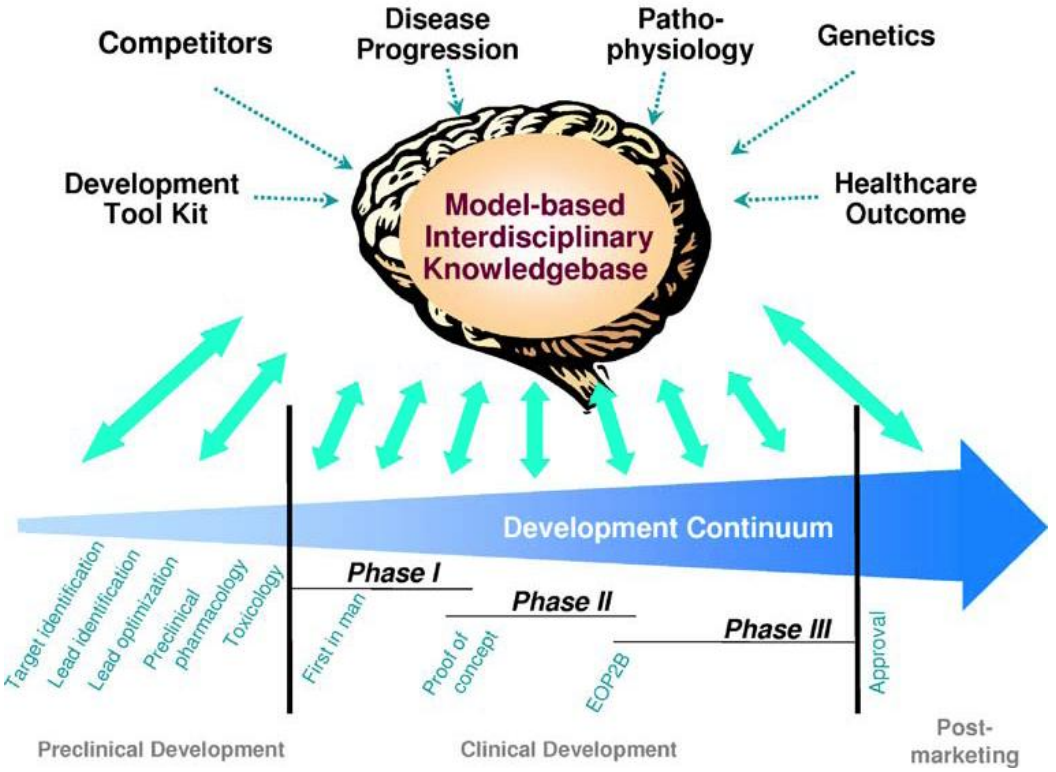
Outline

- Background
- Methodology
- Case studies
- Conclusion

MBDD – Model based drug discovery and development

- **Integrates emerging animal, clinical data and literature to inform decision making process**
- Based upon model based inference
- Key to this, is **robust parameter estimation** and awareness of potential alternative model based explanation of data
- **Structural identifiability and parameter identifiability** is an important step in ensuring this



The development continuum adapted from Zhang L. et al. (2008)

Structural Identifiability

Given postulated state-space model, are the unknown parameters uniquely determined by the output (i.e., perfect, continuous, noise-free data)?

Necessary theoretical prerequisite to:

- Experiment design
- System identification
- Parameter estimation

Formal Definition

Consider following linear system:

$$\dot{x}(t) = A(p)x(t) + B(p)u(t)$$
$$x(0) = x_0(p)$$
$$y(t) = C(p)x(t)$$

p = unknown parameter vector

$p = p_1,..., p_q$, $x = x_1,..., x_i$ $and\ t \geq 0$

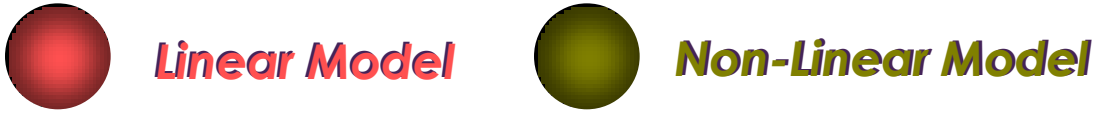
A *uniquely globally identifiable model*
→ a unique set of parameter values (*p*) can be determined by the experiment.

A *locally identifiable model*
→ there exists a finite sets of distinct parameter values (*p*) , which produce the same i/p – o/p.

An *unidentifiable model*
→ there exists an infinite sets of parameter values (*p*) , which produce the same observed behaviour.

SIA methods

1. Laplace-transform approach
2. Taylor series expansion approach
3. Similarity transformation approach



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Similarity Transformation Background – linear model

- For any linear compartmental models, it can be written in the form:

$$\dot{x} = Ax + Bu$$

$$y = Cx$$

where A is the system matrix; B is the input matrix and C is the observation matrix.

Similarity Transformation Method

- **Controllability** ← We can move the model in any direction we like
- **Observability** ← Our observations tell us what is happening internally
- **Existence of Transformation on State Space** ← We can move between two models without any apparent change

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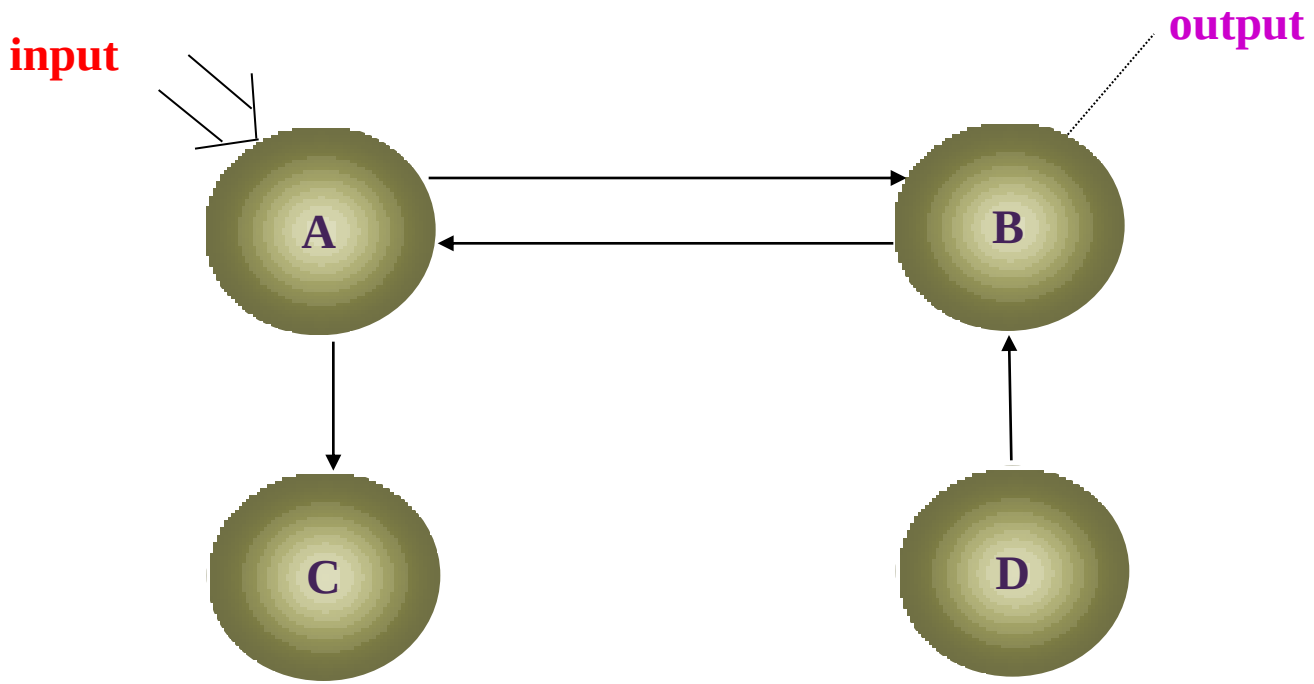
Example

- A,B,C are input connected.
- A,B,D are output connected.
- These are necessary conditions for controllability/observability.
- So D is not controllable and C is not observable (if starting condition is not known).



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“Symptoms of unidentifiability”

- Parameter optimization does not converge.
- Poor %SE when data seems to be reasonable.
- Different estimates dependent upon initial estimate.
- These are all possible indicators of an identifiability issue.

Ways to fix unidentifiable models?

- Increase the number of inputs (dose routes)
- Increase the number of outputs (observations)
- Simplify the model structure
- Reparameterisation/parameter list reductions
- Fix parameters (based on prior knowledge)
- Fit model simultaneously across data sets where some part of the system is know to change : parallel experiments.

Motivations:

- Parameter estimates based on 1 set of data collected from a single experiment – thought to be unidentifiable

- Parameters estimated using 2 sets of data from which the experimental conditions give rise to a perturbation in the values of some of the unknown parameters in the structural model

Targets:

1. Design strategy of experimental design for the types of observation required to get a uniquely identifiable model

2. Design methodology to incorporate this phenomenon to verify the structural identifiability status of the model

Similarity transformation approach

For two linear systems (A, B, C) and $(\tilde{A}, \tilde{B}, \tilde{C})$. If the following conditions are satisfied then the systems have equivalent input-output behaviour.

1. **The two systems are structurally observable.**
2. **The two systems are structurally controllable.**
3. **There exists a non-singular matrix *T* such that the systems are similar:**

$$A = T^{-1}\tilde{A}T, \quad B = T^{-1}\tilde{B}, \quad C = \tilde{C}T$$

Constrained Structures

For a compartmental model $\left(A(p), B(p), C(p)\right)$

The parallel experiments can be expressed by $\left(A'(p'), B'(p'), C'(p')\right)$

where

$$A'(p') = \begin{bmatrix} A(E^1(p')) & 0 & 0 \\ 0 & \cdots & 0 \\ 0 & 0 & A(E^n(p')) \end{bmatrix} \quad B'(p') = \begin{bmatrix} B(E^1(p')) & 0 & 0 \\ 0 & \cdots & 0 \\ 0 & 0 & B(E^n(p')) \end{bmatrix} \quad C'(p') = \begin{bmatrix} C(E^1(p')) & 0 & 0 \\ 0 & \cdots & 0 \\ 0 & 0 & C(E^n(p')) \end{bmatrix}$$

Here $E^i : P' \to P$ for $i = 1 \ldots n$ is a map between the constrained parallel experiment parameters and the individual model parameters.

Notice that

$$dimension(P') < n \cdot dimension(P)$$

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Examples when parallel PK experiments as constrained structure are applicable

- Different oral formulations
- Presence/absence of competitive CYP inhibitor*
- Disease: liver/ kidney impaired
- Gastric emptying

*Duan *et al* 2010 J Clin Pharm

Factor affecting change of PK parameters

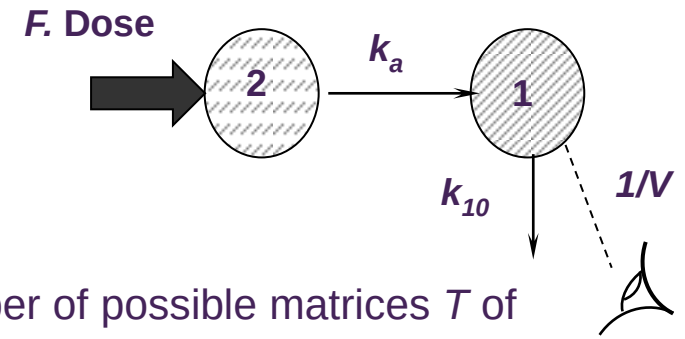
Different oral formulations

- Oral, (tablet, capsulate, solution, emulsion, suspension),
- What affect differentiation to the response if equality of the drug is the same:
  - Excipients (ingredients in addition to additive drug)
  - Manufacturing process
- Different in oral formulation will change the absorption (ka) in the gut and bioavailability (F)

One-compartmental oral model: single experiment

Model written in Matrix form:

$$A=\begin{bmatrix} -k_{10} & k_a \\ 0 & -k_a \end{bmatrix} \quad B=\begin{bmatrix} 0 \\ F \end{bmatrix} \quad C=\begin{bmatrix} \frac{1}{V} & 0 \end{bmatrix}$$



For a given $p=(F,V,k_a,k_{10})$ an infinite number of possible matrices *T* of the form

Transformation matrix $$T=\frac{F}{\tilde{F}}\begin{bmatrix} \frac{k_a}{k_{10}} & 0 \\ \frac{k_{10}-k_a}{k_{10}} & 1 \end{bmatrix}$$

Unidentifiable

For $p_{new}=(V/F,k_a,k_{10})$

$$t_{11}=\frac{V}{\tilde{V}} \qquad \text{and hence} \qquad \frac{k_a}{k_{10}}=\frac{t_{11}}{t_{22}}=\frac{V}{F}\frac{\tilde{F}}{\tilde{V}}$$

The model is thus locally identifiable with two solutions:

$$\left(\frac{V}{F},k_a,k_{10}\right) \text{ and } \left(\frac{Vk_{10}}{Fk_a},k_{10},k_a\right)$$

Locally Identifiable

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One-compartmental model: || experiments

|| experiment structure can be written in Matrix form:

$$A(p') = \begin{bmatrix} -k_{10} & k_a^1 & 0 & 0 \\ 0 & -k_a^1 & 0 & 0 \\ 0 & 0 & -k_{10} & k_a^2 \\ 0 & 0 & 0 & -k_a^2 \end{bmatrix} \quad B(p') = \begin{bmatrix} 0 & 0 \\ F^1 & 0 \\ 0 & 0 \\ 0 & F^2 \end{bmatrix} \quad C(p') = \begin{bmatrix} \frac{1}{V} & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{V} & 0 \end{bmatrix}$$

where $p' = \left(V, k_{10}, k_a^1, k_a^2, F^1, F^2\right)$ and

$$E^1\left(V, k_{10}, k_a^1, k_a^2, F^1, F^2\right) = \left(F^1, V, k_a^1, k_{10}\right)$$
$$E^2\left(V, k_{10}, k_a^1, k_a^2, F^1, F^2\right) = \left(F^2, V, k_a^2, k_{10}\right)$$

Gives

Transformation matrix $T = \frac{F^1}{\tilde{F}^1} \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$

***P'* : Unidentifiable**

However the uniquely identifiable parameter combinations are:

$$p'_{new} = \left(\frac{V}{F^1}, \frac{V}{F^2}, k_a^1, k_a^2, k_{10}\right)$$

Uniquely Identifiable

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Factor affecting change of PK parameters

Presence/absence of competitive CYP inhibitor

- Elimination occurs by excretion (bile, breath, kidney and urine) and metabolism (oxidation, reduction, hydrolysis and conjugation) ~ PhI and II reactions.
- Liver is the major organ for metabolism (other such as kidney, lungs, blood and GI wall)
- Many drugs, oxidation, reduction, enzymes responsible cytochrome (CYP) P450 enzymes CYP1, CYP2, CYP3, each further divided into subfamilies
- Rate of metabolism (CL), bioavaliability (F) and fraction metabolised (fm) by particular enzymes can change

Dextromethorphan (DEX)

- An antitussive agent (OTC).
- Non-opiate properties.
- Active metabolite dextrorphan (DOR), (CYP2D6).
- Data collected form a crossover, randomised and double blinded study.
- DEX placebo, quinidine placebo anteceded at 1 hr.
- DEX (30mg), quinidine placebo anteceded at 1 hr.
- DEX (60mg), quinidine placebo anteceded at 1 hr.
- DEX (30mg), quinidine sulphate 50mg anteceded at 1 hr.
- Plasma and Urine (DEX+DOR)

Moghadamnia, A. et al, J. Clin. Pharmacol. 56:57-67, 2003

Parent-Metabolite Model with Oral Dose

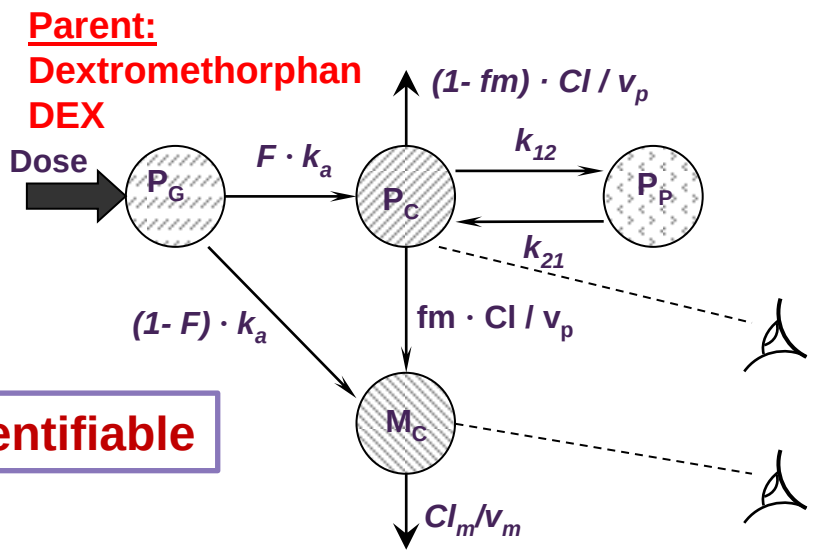
The parameterisation of this model is:

$$p = \left(V_p, V_m, CL_m, k_{12}, k_{21}, k_a, f_m, CL, F\right)$$

The identifiable combination are:

$$p_{new} = \begin{pmatrix} \frac{V_p}{F}, \frac{V_m}{1-F}, \frac{CL}{V_p}, \frac{CL_m}{V_m}, \frac{Ff_m}{1-F}, \\ k_{12}, k_{21}, k_a \end{pmatrix}$$

Unidentifiable



The **|| experiment** using the same model structure was:

1. DEX (30mg), quinidine placebo anteceded at 1 hour
2. DEX (30mg), quinidine sulphate 50mg anteceded at 1 hour

Parameters will remain constant for the two experiments except for those influenced by the rate of metabolism i.e. *F*, *Cl* and f_m.

New parameterisation: $p' = \begin{pmatrix} V_p, V_m, CL_m, k_{12}, k_{21}, k_a, \\ f_m^1, f_m^2, CL^1, CL^2, F^1, F^2 \end{pmatrix}$

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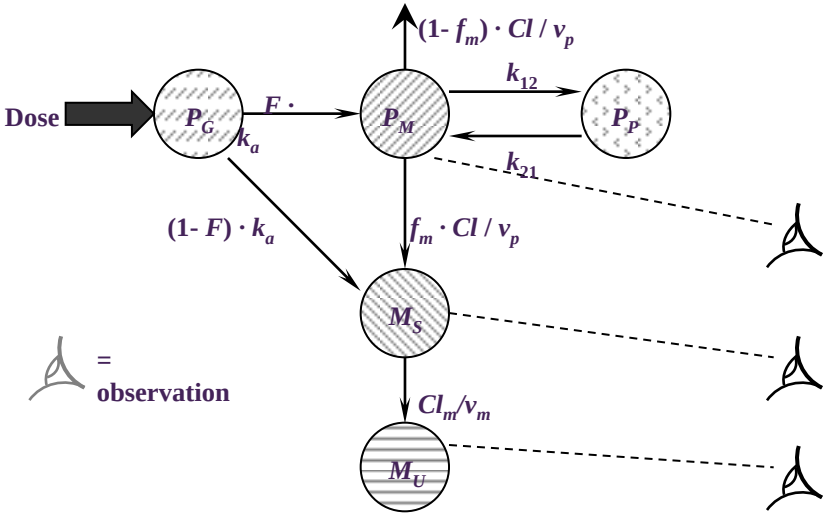
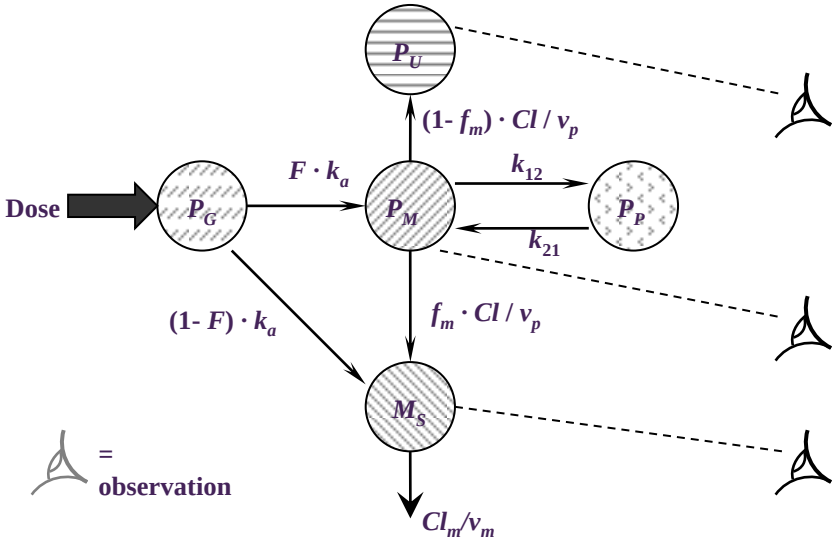
Dextromethorphan (2)





Uniquely Identifiable

Uniquely Identifiable

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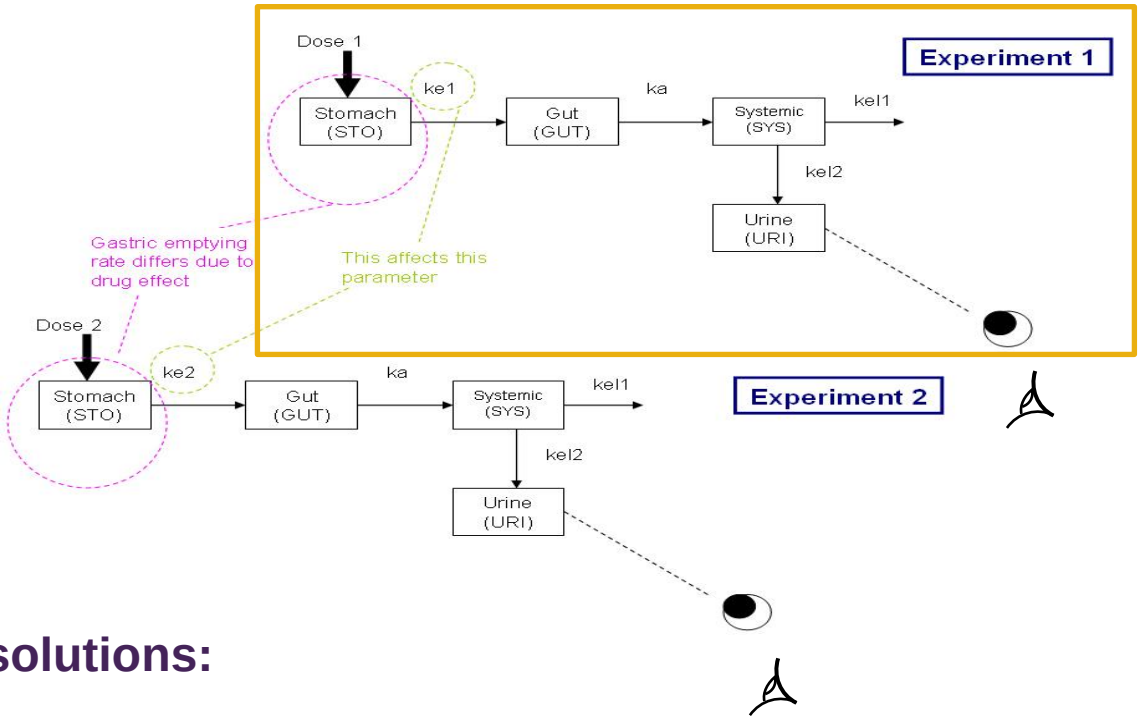
Factor affecting change of PK parameters

Gastric emptying (GE)

- Factor determine the absorption kinetics of a drug following oral administration
- GE rates affected by:
  - Food, e.g. fat (slow GE)
  - Drugs e.g. narcotics (drugs that slow contractions in the intestine)
  - Disease e.g. Diabetes (damage of nerve due to high glucose)
- Rate of gastric emptying rate (ke) will change

GE model

= observation



Locally Identifiable

k_{e1} , k_{e2} = gastric emptying rate
k_a = absorption rate
k_{el1} = non-renal elimination rate
k_{el2} = renal elimination rate

3 solutions:

$kk_{el1} \rightarrow k_{el1}$, $kk_{el2} \rightarrow k_{el2}$, $kk_a \rightarrow k_a$, $kk_{e1} \rightarrow k_{e1}$

(The trivial solution - the parameters are the same)

However, we have extra 2 solutions:

or

$kk_{el1} \rightarrow (k_a.k_{el1})/(k_{el1} + k_{el2})$, $kk_{el2} \rightarrow (k_a.k_{el2})/(k_{el1} + k_{el2})$, $kk_a \rightarrow k_{e1}$, $kk_{e1} \rightarrow k_a$

or

$kk_{el1} \rightarrow (k_{el1}.k_{e1})/(k_{el1} + k_{el2})$, $kk_{el2} \rightarrow (k_{el2}.k_{e1})/(k_{el1} + k_{el2})$, $kk_a \rightarrow k_a$, $kk_{e1} \rightarrow k_{e1}$

$pbar_i = p_i$

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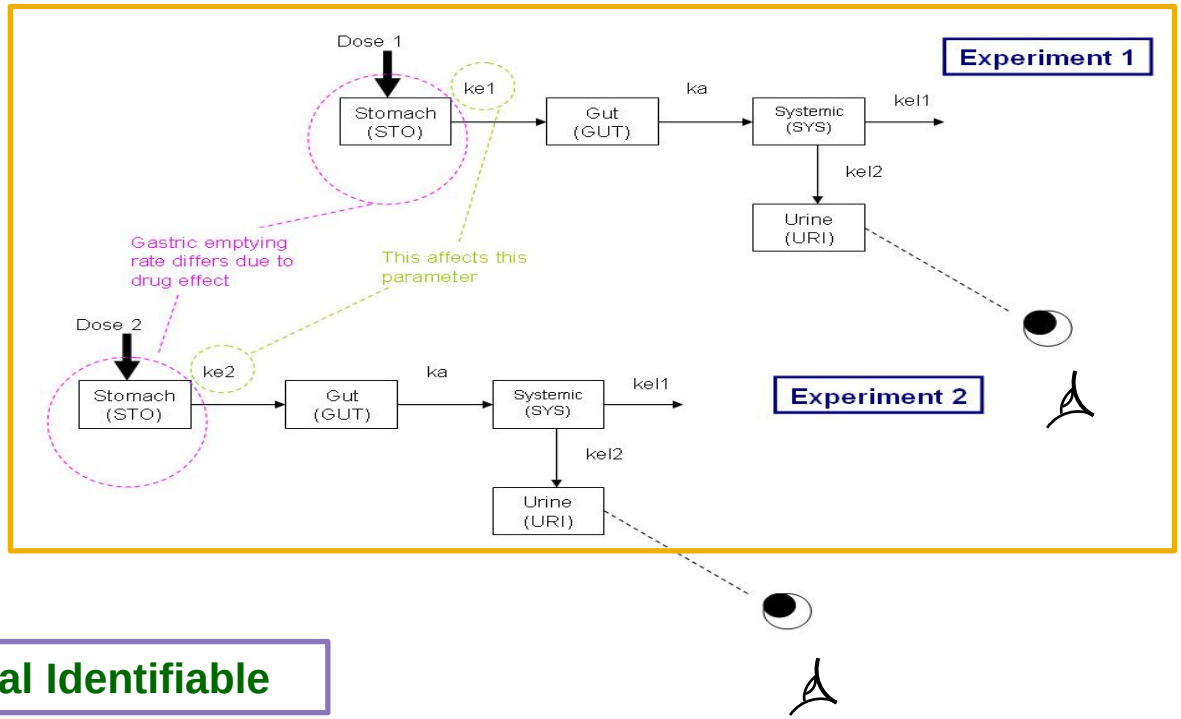
GE model

= observation



Global Identifiable

k_{e1} , k_{e2} = gastric emptying rate
k_a = absorption rate
k_{el1} = non-renal elimination rate
k_{el2} = renal elimination rate

$pbar_i = p_i$

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Conclusion

- Parallel experiments to enhance the structural identifiability of pharmacokinetic models have been implicitly discussed previously (Nelson and Schaldemose 1953; Moghadamnia *et al* 2003).
- A formal formulation and analysis of this experimental design problem
- A preliminary formulation has been presented here that places the concept of a parallel experiment in the context of a single constrained model structure
- 3 case studies have been examined in order to illustrate the constrained model concept.
- Incorporation of prior knowledge into parallel experiment model structures with constrained parameterisation allows sufficient information to be present in the input-output behaviour to give unique parameter estimates.
- It is apparent from the results presented here that parallel experiment strategies can be very powerful in providing globally structurally identifiable pharmacokinetic models.

Remarks

- Globally (unique) identifiability ≠ good fits to experimental data
- The techniques do not required physical data for the analysis but instead symbolic algebra obtained from the model description are manipulated to seek for the identifiability status.
- Lack of identifiability does imply that for every parameter estimate, there will be at least one alternative parameter existed that fit the data sets equally well.
- If a model is unidentifiable, infinite sets of parameters will be found and these will cause difficulties in parameter estimation.
- The analysis is carried out with assistance of symbolic computation software MATHEMATICA, MAPLE etc.
- Limitation will depend on computational power available and skills of analysis
- Structural identifiability analysis is a model validation crucial to experimental design, system identification and parameter estimation, therefore important to MBDD.

Thank you

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